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The statement of the Polish Society of Allergology regarding necessary changes in therapeutic program of severe IgE-mediated allergic asthma with omalizumab

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According to the current (2015) recommendations of Global Initiative for Asthma **(**GINA) dealing under the auspice of World Health Organization (WHO) and in line with registered by EMA in EU as well as in Poland Summary of Product Characteristics (SmPC) [1] Polish Society of Allergology considers, that there is a need of modification of inclusion criteria to Therapeutic Program for treatment of severe IgE-mediated allergic asthma, which is a service guaranteed by National Health Found (NHF) (Table 1 presents the proposals of changes). Currently inclusion criteria are very restrictive, limiting access to the treatment for many groups of patients, especially children, who could benefit from biological treatment. Scientific evidence from clinical [2] as well as observational [3] trials consistently show a significant advantage from early introduction of biological treatment in eligible patients before development of complications resulted from severe course of disease, including airflow limitation, life -threatening exacerbations or adverse reactions after systemic therapy with corticosteroids (CS), among others hypertension, osteoporosis, cataract, glaucoma, metabolic syndrome and diabetes as well as growth inhibition and puberty disorders in children.

Hereby Polish Society of Allergology is requesting as follow:

1. To decrease of age of eligible patients and covered by treatment in Therapeutic Program the children of age between 6 and 12 years, not only older than 12 years as currently. Indications for treatment in this age group exist since 2010, after extended drug registration based on the evidence of efficacy and safety in this group of patients. GINA experts also recommend the treatment with omalizumab in patients over 6 years of age [2].
2. To establish lower threshold for daily dose of inhaled corticosteroids (ICS) on the level of > 400 mcg/day (BDP-CFC) for children at the age between 6–12 years, according to the table of equivalent doses of ICS, developed by GINA experts, in which the doses > 400 mcg/day in that age group are already considered as high (Box 3−6, pp 32) [1].
3. To remove criterion „Common previous using of oral CS (OCS), including past 6 months", because there is no such a prerequisite for treatment with omalizumab neither in GINA recommendations [1] nor SmPC [2]. Moreo-

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ver, GINA experts prefer omalizumab as add-on-therapy to the grade 4 treatment rather than chronic administration of low doses of OCS [1]. According to the current Program, the prerequisite indicated by Program Coordinating Committee is taking a minimum mean daily dose of OCS calculated from previous 6 months of 5 mg of equivalent dose of prednisone [5], which practically excludes patients without chronic administration of OCS. According to the GINA experts' highlights and clinical trials evidence, chronic administration of OCS, even in low doses, constitutes a significant risk of serious adverse systemic reactions [1]. At the time being the aim of asthma therapy is not only current symptoms control, but minimizing of future risk, including the risk of therapy adverse reactions [1]. Hence, it seems to be appropriate to use primarily the treatment with possible lower risk of serious adverse reactions to save future suffer of patients and to decrease of cost resulted from treatment of complications.

4. To modify the recommendations regarding treatment of severe exacerbations. In their novel recommendation GINA experts highlighted that short courses of OCS could be replaced by high doses ICS [1][1]. Inhaled route of corticosteroids administration is always safer than oral, taking into consideration lower systemic exposure, leading to the lower risk of after-steroids complications. This is extremely important in group of patients susceptible for systemic CS, such as children and adolescent as well as diabetic patients, with metabolic syndrome, osteoporosis and other serious complications after CS therapy. If, according to the treating physician's opinion, there is more beneficial to use in the first line the nebulization with high doses of ICS in a patients due to high risk of steroids adverse reactions, this therapy should be accepted, as there is evidence of its clinical equivalence compare to OCS [6–9]. According to the suggestions of Polish Society of Allergology experts, nebulization with ICS dose of over 2000 mcg/day should be considered as clinically relevant. Additionally, one should remember about the patients who continuously take systemic CS in order to prevent the exacerbations. Chronic therapy with OCS is heavily burdened with the risk of adverse reactions. Introduction of biological therapy for this group of patients gives a chance for limiting of demand of OCS, and sometimes even permanent discontinuation of that therapy [10–12].
5. To increase the spirometric threshold from < 60% of expected value < 80% of expected value or to the best personal value for the patients older than 12 years, and to not establish any spirometric criterion for children between 6–12 years. This is in line in SmPC statement [2]. In the recent revision of their guidelines GINA experts removed the spirometric criterion from current asthma control [1], therefore it is not taken into consideration during treatment schedule planning, and omalizumab itself has no bronchodilating effect and improvement of lung function is not an expected result of treatment. Decreasing of lung function below 60% of expected value is a future high risk factor and is commonly observed in patients with long-lasting severe asthma, in which obstructive changes resulted from remodeling are irreversible. The aim of treatment of patients within Therapeutic Program should be prevention of such states rather than waiting for severe airway limitation, hence the increasing of threshold to < 80% as in SmPC seems to be justified.
6. To leave other criteria without any changes.

It should be clearly emphasized, that the introduction of Therapeutic Program of treatment of severe IgE-mediated asthma in 2013 and reimbursement from public sources was an indubitable success of Country Consultant for Allergology, Polish Society of Allergology, covering allergologists and patients suffering from severe asthma, with their continuous efforts as well as Ministry of Health and National Health Found. This program enabled wider access to biological treatment for patients with severe asthma and moved Poland closer to the standards accepted in other UE countries. Each and every patient, who meets inclusion criteria can be treated within the program, without any restrictions of eligible patient's' number. Currently there are 372 patients within the program. Since the beginning of the Program only 40 patients were excluded from treatment due to lack of significant improvement or other reasons, which confirms the high clinical effectiveness of the drug [13]. Therefore, making available this treatment to the bigger group of patients with severe asthma could give a chance for better quality of life to bigger number of patients as well as their families, and it could limit the healthcare system burden connected to

Table 1. Summary of suggested by Polish Society of Allergology changes to the inclusion Criteria of Therapeutic Program of treatment of severe IgE-mediated asthma

Current Program inclusion criteria	Suggested Program inclusion criteria	Base of modification
1. Patients older than **12 years** with severe, uncontrolled allergic asthma (**according GINA 2009**) with allergy to perennial aeroallergen, confirmed by SPT or sIgE	1. Patients older than **6 years** with severe, uncontrolled allergic asthma (**according GINA 2015**) with allergy to perennial aeroallergen, confirmed by SPT or sIgE	SmPC
2. Demonstrating the clear reactivity *in vitro* (RAST) to perennial aeroallergen in patients with total IgE serum concentration below 76 IU/ml	2. Demonstrating the clear reactivity *in vitro* **(RAST ELISA)** to perennial aeroallergen in patients with total IgE serum concentration below 76 IU/ml	
3. The need to administer high doses of ICS **(> 1000 mcg BDP CFC/day)** in combination with other asthma controlling drug (LABA, LTRA, theophylline derivatives)	3. The need to administer high doses of ICS **(> 1000 mcg BDP CFC/day in adults and > 400 mcg/day in children 6–12 years)** in combination with other asthma controlling drug (LABA, LTRA, theophylline derivatives)	GINA
4. Common previous administration of oral CS, including last 6 months	4. Point removed	GINA, SmPC
5. Meeting at least 3 following criteria:	5. Meeting at least 3 following criteria:	
a) The symptoms of uncontrolled asthma (lack of asthma control in asthma control test ACQ > 1.5 points)	a) The symptoms of uncontrolled asthma (lack of asthma control in asthma control test ACQ > 1.5 points)	
b) 3 or more episodes of exacerbations during the year, requiring administration of systemic CS **or increasing the doses in patients using them permanently**	b) 3 or more episodes of exacerbations during the year, requiring administration of systemic CS **or high doses of CSI in nebulization >2000 mcg/day in equivalence to BUD or a need to continuous administer systemic CS (≥ 5 mg/day in in equivalence to prednisone) in order to prevent the exacerbations of disease**	GINA
c) Hospitalization during previous 12 months due to exacerbation of asthma	c) Hospitalization during previous 12 months due to exacerbation of asthma	
d) Previous life-threating asthma attack	d) Previous life-threating asthma attack	
e) Continuous airways obturation (forced expiratory volume in one second **FEV_1 < 60% of expected value** or daily changes of peak expiratory flow PEF > 30%)	e) Continuous decreasing of lung function **(FEV1 < 80% of expected value or the best value) in patients ≥ 12 years**	SmPC
f) Asthma-related decreasing of quality of life (mean score in asthma quality of life control test AQLQ < 5.0 points)	f) Asthma-related decreasing of quality of life (mean score in asthma quality of life control test AQLQ < 5.0 points)	
6. Total IgE serum concentration 30–1500 IU/ml	6. Total IgE serum concentration 30–1500 IU/ml	
7. Body mass 20–150 kg	7. Body mass 20–150 kg	
8. Non-smoking	8. Non-smoking	
9. Exclusion of underlined mechanisms (concomitant diseases) leading to severe course of asthma other than body reaction on perennial aeroallergen	9. Exclusion of underlined mechanisms (concomitant diseases) leading to severe course of asthma other than body reaction on perennial aeroallergen	

CS – corticosteroid, ICS — inhaled corticosteroid, SmPC — Summary of Product Characteristics GINA— Global Initiative for Asthma; SPT — skin prick-testing; RAST — radioallergosorbent test; LABA — long acting beta agonist; LTRA — leukotriene receptor antagonists; ACQ — Asthma Control Questionnaire; FEV1 — forced expiratory volume in one second; AQLQ — Asthma Quality of Life Questionnaire

the treatment of disease acute exacerbations and adverse reactions of therapy with CS. Estimated number of patients with severe asthma, eligible to immunological criteria according to the program Criteria is app. 1000 [14], so there is no expectations of uncontrolled increasing of number of program's participants after introduction of suggested changes.

Conflict of interest

The authors declare no conflict of interest.

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